

ORIGINAL ARTICLE

Timing and Magnitude of Increases in Levothyroxine Requirements during Pregnancy in Women with Hypothyroidism

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ABSTRACT

BACKGROUND

Hypothyroidism during pregnancy has been associated with impaired cognitive development and increased fetal mortality. During pregnancy, maternal thyroid hormone requirements increase. Although it is known that women with hypothyroidism should increase their levothyroxine dose during pregnancy, biochemical hypothyroidism occurs in many. In this prospective study we attempted to identify precisely the timing and amount of levothyroxine adjustment required during pregnancy.

METHODS

Women with hypothyroidism who were planning pregnancy were observed prospectively before and throughout their pregnancies. Thyroid function, human chorionic gonadotropin, and estradiol were measured before conception, approximately every two weeks during the first trimester, and monthly thereafter. The dose of levothyroxine was increased to maintain the thyrotropin concentration at preconception values throughout pregnancy.

RESULTS

Twenty pregnancies occurred in 19 women and resulted in 17 full-term births. An increase in the levothyroxine dose was necessary during 17 pregnancies. The mean levothyroxine requirement increased 47 percent during the first half of pregnancy (median onset of increase, eight weeks of gestation) and plateaued by week 16. This increased dose was required until delivery.

CONCLUSIONS

Levothyroxine requirements increase as early as the fifth week of gestation. Given the importance of maternal euthyroidism for normal fetal cognitive development, we propose that women with hypothyroidism increase their levothyroxine dose by approximately 30 percent as soon as pregnancy is confirmed. Thereafter, serum thyrotropin levels should be monitored and the levothyroxine dose adjusted accordingly.

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PRIMARY HYPOTHYROIDISM IS COMMON, occurring in 3 to 10 percent of women, frequently with its onset during the child-bearing years.^{1,2} An estimated 1 to 2 percent of all pregnant women receive levothyroxine therapy for hypothyroidism. Epidemiologic studies indicate that 0.4 percent of pregnant women have serum thyrotropin concentrations above 10 μ U per milliliter at 15 to 18 weeks of gestation.^{3,4} Thus, in the United States alone, a minimum of 12,000 to 16,000 infants are born each year to women with either inadequately treated or undiscovered primary hypothyroidism.^{5,6}

During pregnancy, women's thyroid physiology undergoes well-defined changes, including an approximate doubling in thyroxine-binding globulin concentrations due to increases in estradiol concentrations, as well as a 30 to 40 percent increase in plasma volume.⁷⁻¹¹ These changes result in a significant increase in the total thyroxine pool, primarily during the first trimester. This increment may be provided largely by thyroid stimulation induced by human chorionic gonadotropin,^{7,8,10} since a slight increase in free thyroxine and a reduction in thyrotropin occur at 9 to 12 weeks of gestation.^{8,12} In general, however, the thyrotropin concentration stays within the normal range for the remainder of pregnancy, despite the estimated 30 to 50 percent increase in the levothyroxine requirement.^{9,10,13-15}

Although this process is now recognized by endocrinologists and some hypothyroid patients are alerted to the need for such an increase, many pregnant women are found to have a high serum thyrotropin concentration at the time of their initial obstetrical examination, at 8 to 12 weeks of gestation.^{3,4,10,13,16-22} Thus, current practice permits a transient period of maternal hypothyroxinemia in the first trimester, which is a time when the free thyroxine concentration is typically slightly increased. It is known that the pregnant woman is the sole source of the fetal supply of thyroid hormones from conception to approximately 13 weeks of gestation when fetal thyroid function has developed. Given the possible association between gestational hypothyroidism and impaired intellectual and cognitive development in offspring, as well as the increased rate of fetal death in women with an elevated thyrotropin concentration,^{3,20,23,24} the current approach is suboptimal.

In this prospective study, we sought to delineate the precise timing and pattern of the increased thyroid hormone requirement during pregnancy in or-

der to determine appropriate recommendations for preventing first-trimester hypothyroidism. We used a strategy involving frequent monitoring of serum thyrotropin concentrations with concomitant adjustments in the dose of levothyroxine to maintain thyrotropin at preconception concentrations.

METHODS

Women with primary hypothyroidism who desired pregnancy were recruited from the endocrine outpatient clinics at Brigham and Women's Hospital, Boston (Table 1). Maternal thyroid function, estradiol, and human chorionic gonadotropin were measured before and during pregnancy. Our goal was to assess biochemical thyroid status after the first missed menstrual cycle, every two weeks throughout the first trimester, and monthly thereafter until the completion of the pregnancy. This aim was achieved in most, but not all, subjects.

At each visit, two aliquots of serum were obtained. The first was frozen and saved for batch analysis at the completion of the study. The second was analyzed immediately to determine the thyrotropin concentration (normal range, 0.5 to 5.0 μ U per milliliter) and free thyroxine index. The dose of levothyroxine was adjusted as needed, usually in 25- μ g increments, to maintain the thyrotropin concentration at preconception values.

Six of the subjects had a history of thyroid cancer; in these subjects, the levothyroxine dose was adjusted when the thyrotropin concentration was greater than 0.5 μ U per milliliter. For all the others, the levothyroxine dose was adjusted if the thyrotropin concentration was greater than 5.0 μ U per milliliter. Specifically, the levothyroxine dose was increased by 25 μ g in all the subjects whenever initial blood testing revealed thyrotropin concentrations above the target range. Thereafter, the dose of levothyroxine was increased by 12.5 μ g if subsequent thyrotropin values were between 5 and 10 μ U per milliliter (or 0.5 to 5.0 μ U per milliliter, in subjects with a history of thyroid cancer) and by 25 μ g if subsequent thyrotropin values were greater than 10 μ U per milliliter (or greater than 5.0 μ U per milliliter, in subjects with a history of thyroid cancer). After delivery, levothyroxine was given in the doses used before conception. All the subjects returned for a repeated set of thyroid-function tests six weeks after delivery.

The subjects were instructed not to ingest any vitamins or products containing calcium, iron, or soy within four hours before or after the time they in-

Table 1. Descriptive Characteristics of 19 Women Followed Prospectively during Pregnancy.

Subject	Age	Cause of Hypothyroidism*	Baseline Thyrotropin	Baseline Thyroxine Dose		Increase in Thyroxine Dose during Gestation	Outcome of Pregnancy
	yr		$\mu\text{U/mL}$	$\mu\text{g/day}$	$\mu\text{g/kg/day}$	%	
1	32	Treatment for benign thyroid nodule	1.70	125	1.9	20	Full-term delivery
2	31	Treatment for Graves' disease	0.91	125	2.1	40	Full-term delivery
3	33	Hashimoto's disease	0.59	100	1.6	37	Full-term delivery
4	32	Hashimoto's disease	0.56	137	2.1	46	Full-term delivery
5†	27	Treatment for Graves' disease	0.67	88	1.5	27	Miscarriage at 14 wk
5	28	Treatment for Graves' disease	0.42	88	1.5	45	Full-term delivery
6	39	Hashimoto's disease	1.38	175	2.4	29	Full-term delivery
7	34	Hashimoto's disease	2.78	88	1.4	57	Full-term delivery
8‡	34	Hashimoto's disease	1.24	112	1.9	56	Full-term delivery
9‡	40	Treatment for benign thyroid nodule	1.21	128	1.6	56	Stillbirth twin gestation at 21 wk
10‡	40	Treatment for Graves' disease	3.69	75	1.5	85	Full-term delivery
11	33	Treatment for thyroid cancer	0.10	150	2.4	55	Full-term delivery
12	37	Treatment for thyroid cancer	0.03	150	2.6	67	Full-term delivery
13	30	Treatment for thyroid cancer	0.09	175	2.5	29	Full-term delivery
14	32	Treatment for thyroid cancer	0.01	175	2.4	50	Full-term delivery
15	31	Treatment for thyroid cancer	0.08	137	2.6	46	Full-term delivery
16	31	Treatment for thyroid cancer	0.04	175	2.7	43	Pregnancy terminated at 16 wk
17	33	Hashimoto's disease	1.61	63	1.0	0	Full-term delivery
18	37	Hashimoto's disease	1.82	75	1.3	0	Full-term delivery
19	31	Hashimoto's disease	2.87	150	1.2	0	Full-term delivery

* Treatment for nonmalignant thyroid nodules consisted of subtotal thyroidectomy; treatment for Graves' disease consisted of iodine-131 ablation, and treatment for thyroid cancer consisted of near-total thyroidectomy and iodine-131. For patients with Graves' disease or benign thyroid nodules, the target thyrotropin concentration was less than 5.0 μU per milliliter, and for patients with thyroid cancer, the target thyrotropin concentration was less than 0.5 μU per milliliter.

† The subject became pregnant twice.

‡ The subject became pregnant by means of assisted-reproduction techniques.

gested their levothyroxine. The date of conception was estimated to be 2 weeks after the last menstrual period, and the gestational age was confirmed by fetal ultrasound examination at 16 weeks.

Analytic measurements of thyrotropin, thyroxine, triiodothyronine, free thyroxine, and human chorionic gonadotropin were performed with the use of a Bayer Advia Centaur analyzer. The thyroid hormone-binding ratio was determined by means of a normalized, two-step, competitive immunoassay version of a triiodothyronine-uptake assay.²⁵ The result was normalized to serum samples containing normal concentrations of thyroxine and thyroxine-binding globulin. The free thyroxine index is the product of the thyroid hormone-binding

ratio and the total thyroxine value, with a normal range of 5.0 to 11.0. Similarly, the free triiodothyronine index is the product of the thyroid hormone-binding ratio and the total triiodothyronine value, with a normal range of 70 to 170. The free-thyroxine assay is a direct competitive immunoassay in which the subject's thyroxine competes with a tagged thyroxine analogue for a limited amount of polyclonal rabbit anti-thyroxine antibody. At the time of batch analysis, specimens were thawed, mixed, and analyzed within two hours. Specimens were not diluted except for those with human chorionic gonadotropin values above 1000 U per liter, which were automatically diluted to 1:200.

Permission to perform this investigation was

granted by the Brigham and Women's Hospital institutional review board. All the participants gave their written informed consent.

STATISTICAL ANALYSIS

Descriptive statistical data were compared with use of the Wilcoxon rank-sum test (for continuous data) or the chi-square test (for categorical data) and are presented according to subject or pregnancy, as appropriate. Changes in the results of thyroid-function tests, human chorionic gonadotropin and estradiol concentrations, and levothyroxine doses throughout pregnancy were graphed with the use of locally weighted polynomial regression to achieve the best-fit curve throughout pregnancy, with no attempt to document statistical significance. To assess the statistical significance of changes in various response variables during pregnancy, the results before pregnancy and at 10, 20, 30, and 38 weeks of gestation were analyzed by repeated-measures analysis of variance and by post hoc subgroup comparisons with use of the Newman-Keuls test. All data were analyzed with the use of SPSS software, version 11.0. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Nineteen women became pregnant; one became pregnant twice, and three became pregnant by assisted reproductive techniques. Overall, there were 20 pregnancies and 17 term deliveries (Table 1). The serum thyrotropin level increased during the first 10 weeks of gestation, prompting an increase in the levothyroxine dose in 85 percent of the group, including all the athyreotic subjects (Fig. 1 and Table 2). An increase in the total thyroxine and triiodothyronine concentrations compensated for the decrease in the free hormone fraction, as reflected in the decreased thyroid hormone-binding ratio. The prescribed increments in levothyroxine (mean, 29 percent at 10 weeks), however, did not reproduce the typical increase in the free thyroxine index (and decrease in thyrotropin) that normally occur at the approximate time of the human chorionic gonadotropin peak. Both the free thyroxine index and the concentration of free thyroxine were constant throughout pregnancy ($P=0.33$) (Fig. 1 and Table 2).⁷⁻⁹

In subjects without a history of thyroid cancer who required an increase in the dose of levothyroxine during pregnancy, the mean (\pm SD) thyrotropin

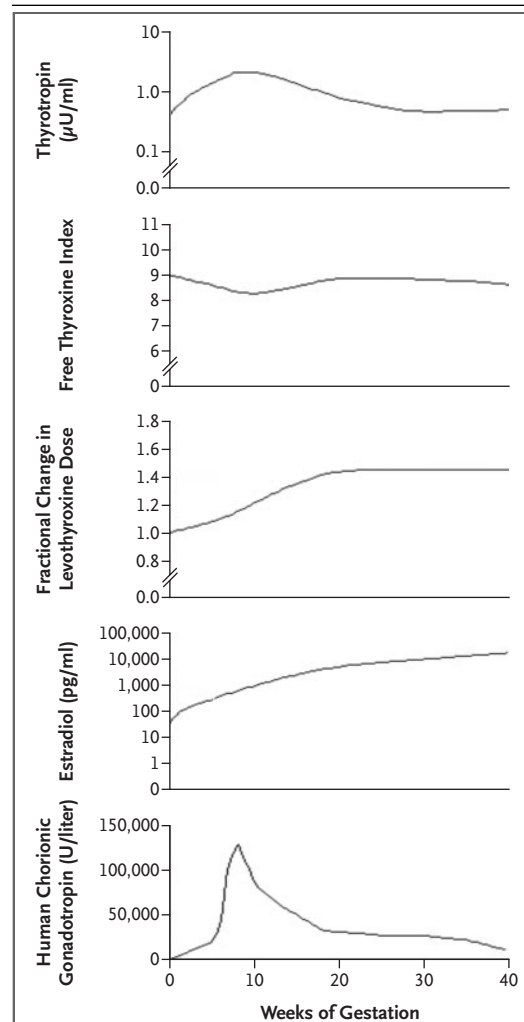


Figure 1. Changes in Maternal Hormone Concentrations and the Levothyroxine Dose during Gestation.

The graphs depict the best-fit curves for serum thyrotropin (range, 0.5 to 5.0 μ U per milliliter), the free thyroxine index (range, 5 to 11), the fractional increase in the dose of levothyroxine, the maternal estradiol concentration (range, 10 to 80 pg per milliliter), and the concentration of human chorionic gonadotropin (range, less than 5 U per liter) throughout pregnancy in the 14 women who required an increase in the levothyroxine dose during a full-term pregnancy. To convert the values for estradiol to picomoles per liter, multiply by 3.67.

concentration before pregnancy was 1.5 ± 1.1 μ U per milliliter, and at 38 weeks of gestation it was 1.4 ± 0.3 μ U per milliliter ($P=0.92$). In subjects with a history of thyroid cancer, the mean thyrotropin concentration before pregnancy was 0.05 ± 0.04 μ U per milliliter, and at 38 weeks of gestation it was 0.06 ± 0.04 μ U per milliliter ($P=0.99$). One woman required a

Table 2. Serum Values before and during Gestation in All Women Who Required an Increase in the Dose of Levothyroxine during Gestation.*

Variable	Week of Gestation				P Value by ANOVA		P Value by Newman-Keuls Test			
	Before Pregnancy	10	20	30	38	Before Pregnancy vs. 10 wk	Before Pregnancy vs. 20 wk	Before Pregnancy vs. 38 wk	10 wk vs. 20 wk	20 wk vs. 38 wk vs. 38 wk
Thyrotropin ($\mu\text{U/ml}$)	1.0 \pm 1.14	4.2 \pm 3.8	2.3 \pm 3.2	1.3 \pm 1.5	1.0 \pm 0.9	<0.01	0.002	0.29	0.04	0.28 0.93
Free thyroxine index	8.8 \pm 1.2	7.8 \pm 1.8	8.9 \pm 1.5	8.5 \pm 1.7	8.5 \pm 1.8	NA	0.33	NA	NA	NA
Thyroid hormone-binding ratio	1.0 \pm 0.1	0.8 \pm 0.1	0.7 \pm 0.05	0.6 \pm 0.06	0.6 \pm 0.1	<0.001	<0.001	<0.001	<0.001	0.79 0.99
Thyroxine dose (fraction of dose before pregnancy)	1.00 \pm 0	1.29 \pm 0.25	1.48 \pm 0.18	1.48 \pm 0.15	1.47 \pm 0.17	<0.001	<0.001	<0.001	<0.001	0.99 0.99
Estradiol (pg/ml)	55 \pm 24	1100 \pm 400	7000 \pm 2800	13,500 \pm 3500	20,400 \pm 4200	<0.001	<0.001	<0.001	<0.001	<0.001 <0.001 <0.001

* Plus-minus values are means \pm SD. To convert the values for estradiol to picomoles per liter, multiply by 3.67. ANOVA denotes analysis of variance, and NA not applicable.

decrease of 12.5 μg in the levothyroxine dose at 26 weeks to maintain goal thyrotropin concentrations thereafter.

The best-fit curve for the levothyroxine dose shows a rapid increase between 6 and 16 weeks of gestation and a subsequent plateau (Fig. 1). At 10 weeks of gestation, the levothyroxine dose had increased by 29 \pm 25 percent as compared with the dose at baseline ($P<0.001$). At 20 weeks, the increase relative to baseline was 48 percent ($P<0.001$), but the dose remained stable thereafter (Table 2). The changes during the first half of pregnancy were chronologically associated with a rapid decrease in the thyroid hormone-binding ratio, reflecting the estradiol-induced increase in serum concentrations of thyroxine-binding globulin. Notably, the thyroid hormone-binding ratio decreased most rapidly when the levothyroxine requirement increased most rapidly. Both remained nearly unchanged between 20 and 38 weeks. However, estradiol concentrations increased exponentially throughout pregnancy (Fig. 1 and Table 2).

The time at which an increased thyrotropin concentration was first observed varied between 4.4 and 16.0 weeks of gestation (median, 8 weeks) (Fig. 2). This observation was similar in subjects with a history of thyroid cancer and those without such a history. Nine of 17 subjects (53 percent) had a thyrotropin increment of greater than 1 μU per milliliter at the time of their first visit (mean, five weeks of gestation). The three subjects who became pregnant by means of assisted reproductive techniques appeared to have a greater increase in thyrotropin early during gestation than those with spontaneous pregnancies (Fig. 3A). Serum estradiol concentrations at seven weeks of gestation were significantly higher in subjects who had become pregnant by assisted reproduction (1506 \pm 460 pg per milliliter [5527 \pm 1688 pmol per liter]) than the concentrations in the subjects who became pregnant spontaneously (484 \pm 265 pg per milliliter [1776 \pm 973 pmol per liter], $P<0.01$).

That estradiol plays an important role in the increase in the levothyroxine requirement during pregnancy was also implied by the data from Subject 5, who conceived twice during the study. Her first pregnancy ended in spontaneous abortion at 14 weeks, and her second was a full-term pregnancy. Her levothyroxine requirements, in conjunction with her serum estradiol concentrations, increased at a similar time point and to a greater extent during her second pregnancy (Fig. 3B).

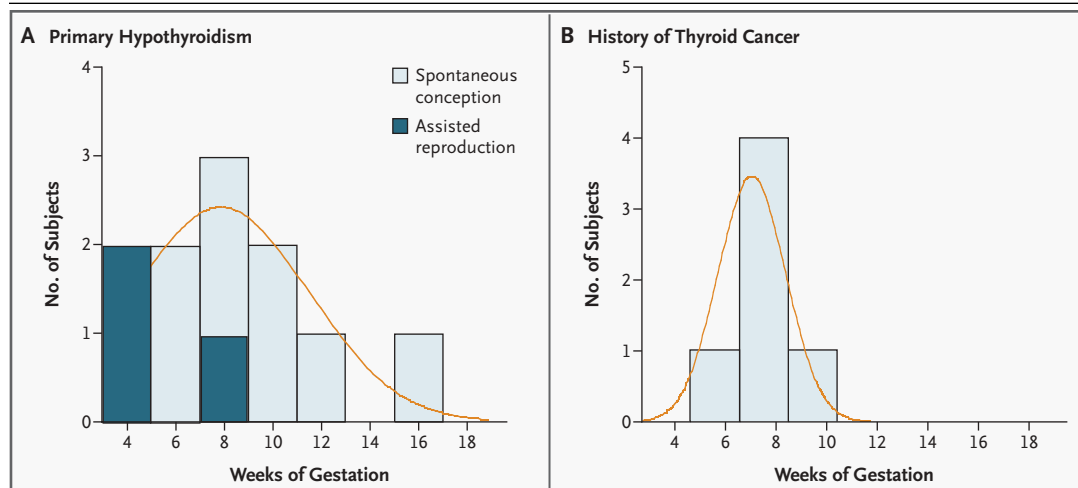


Figure 2. Gestational Week of the Initial Increase in the Levothyroxine Dose.

Panel A shows the week at which the levothyroxine dose was first increased in 11 women with primary hypothyroidism; in these women, the dose was increased when the thyrotropin concentration was greater than 5.0 μU per milliliter. Panel B shows the week at which the levothyroxine dose was first increased in women with a history of thyroid cancer; in these women, the dose was increased when the thyrotropin concentration was greater than 0.5 μU per milliliter.

Within two weeks after delivery, all the subjects resumed taking their prepregnancy dose of levothyroxine. Fourteen subjects returned for testing six to eight weeks after delivery. Thyrotropin concentrations had returned to prepregnancy values in all of them.

DISCUSSION

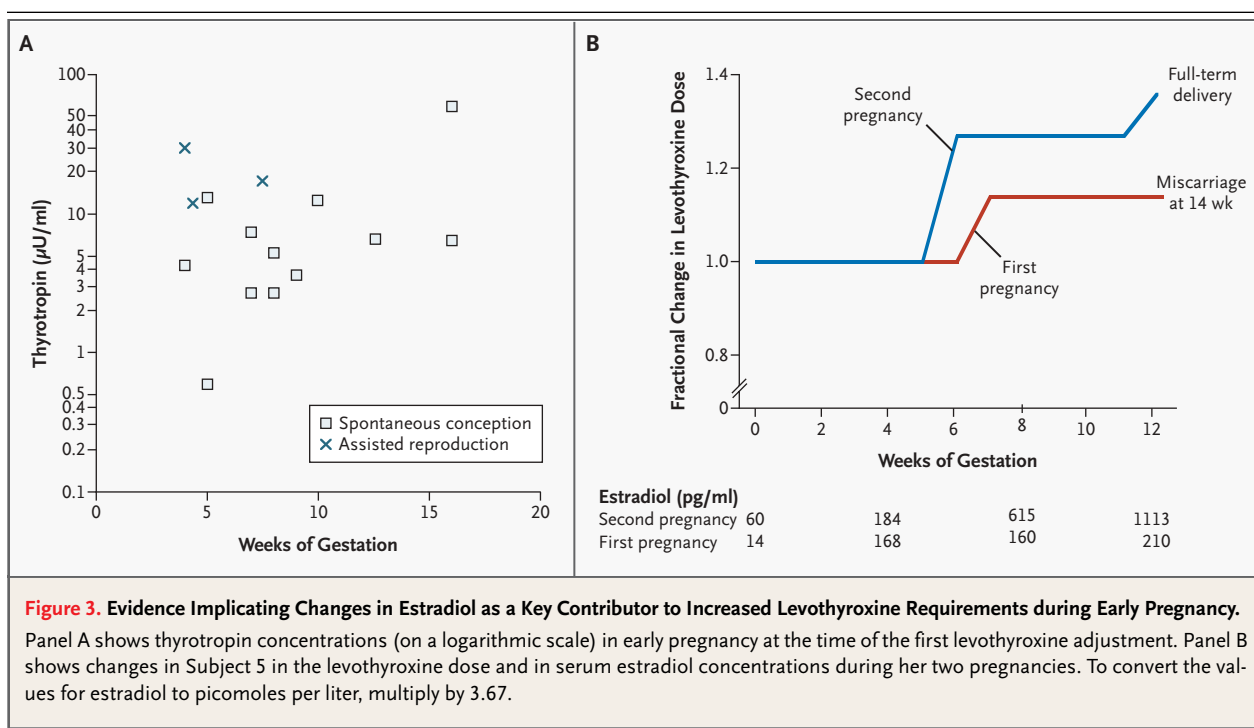
This prospective study indicates that frequent testing in association with frequent adjustments in the dose of levothyroxine can be used to estimate when levothyroxine requirements increase during pregnancy, and by how much. Levothyroxine requirements increased in 85 percent of the cohort. In these subjects, a mean increase of 47 percent was necessary to maintain the thyrotropin concentration at a prepregnancy value. The required levothyroxine dose increased during the first 16 to 20 weeks of gestation but plateaued thereafter.

In normal pregnancy, there is a physiologic increase in free thyroxine and a decrease in thyrotropin, and these changes are maximal at the time the human chorionic gonadotropin concentration peaks (approximately 10 to 12 weeks of gestation).^{7-9,12} In our subjects, we did not observe this increase. Rather, there was a peak in the thyrotropin concentration at about 8 to 10 weeks of gestation, accompanied by a downward trend in the free

thyroxine index. These results suggest that an important role of the human chorionic gonadotropin–thyroid axis in healthy women is to increase the thyroid hormone pool during the first trimester.

We did not directly quantitate the changes in thyroxine-binding globulin, since this variable has already been thoroughly studied.⁸ A rapid increase in unoccupied binding sites on this molecule can be inferred from the decrease in the thyroid hormone-binding ratio (a surrogate for the free fraction of triiodothyronine or thyroxine) during the first 20 weeks of gestation. The cause of the increase in thyroxine-binding globulin appears to be twofold: clearance decreased because of estradiol-altered hepatic glycosylation of thyroxine-binding globulin²⁶ and an estradiol-induced increase in synthesis.¹⁴ During the second half of pregnancy, while serum estradiol continues to increase, there are only small increases in thyroxine-binding globulin⁸ and small decreases in the thyroid hormone-binding ratio. While other changes that could increase levothyroxine requirements occur early in pregnancy, the fact that estradiol causes sustained increases in thyrotropin concentrations, levothyroxine requirements, or both in hypothyroid women after menopause indicates that an elevated estradiol concentration per se is sufficient to cause this change.²⁷

The possibility that increases in estradiol levels constitute a key etiologic factor in the need to in-



crease the levothyroxine dose is also supported by our observation that subjects who had undergone assisted reproduction had earlier and relatively greater increases in serum levels of thyrotropin and estradiol than those who had conceived spontaneously. In addition, the increased levothyroxine requirement was noted during a successful, full-term pregnancy in one woman in whom a blunted increase in estradiol and levothyroxine requirements had been observed during a first, unsuccessful pregnancy. Furthermore, a slight increase in thyrotropin and a reduction in free thyroxine have been documented during assisted reproduction, even in women who have an intact thyroid.²⁸ Thus, it is clear that assisted reproduction, probably because it involves a rapid increase in plasma estradiol concentrations, places a severe strain on the hypothalamic–pituitary–thyroid axis.

This analysis suggests that during the first half of pregnancy, thyroxine production (or levothyroxine intake) must exceed its metabolic clearance until the pool of thyroxine is large enough to allow normalization of free thyroxine and triiodothyronine, despite a high concentration of thyroxine-binding globulin. This phenomenon, first described more than a decade ago,^{10,13} may be due to a number of factors.

Increases in thyroxine-binding globulin are a possible contributor early in pregnancy, but the concentration of this protein plateaus by 20 weeks, as reflected in the stable thyroid hormone-binding ratio. Thus, this factor cannot explain the persistent increase in the levothyroxine requirement. A recent report of a similar fractional increase in the levothyroxine dose during pregnancy in a woman with partial deficiency in thyroxine-binding globulin supports this contention.²² Furthermore, a high concentration of thyroxine-binding globulin alone does not reduce the availability of thyroxine or triiodothyronine, since the free thyroxine and thyrotropin concentrations are normal throughout the second half of pregnancy.⁹

Additional factors, some of which may also be present during the first half of pregnancy, may contribute to the increased requirement. They include increased inactivation of triiodothyronine and thyroxine by type 3 iodothyronine deiodinase, which is widespread in the human fetoplacental unit and uterus, increases throughout pregnancy, and, at least in rats, may be augmented by estradiol.^{29,30} Maternal thyroxine and triiodothyronine are transferred to a congenitally hypothyroid fetus, but it is thought that this process does not take place when fetal thyroid function is normal.³¹ In addition, there

is a continuous increase in maternal plasma volume that lasts into the third trimester, but the pattern of changes correlates poorly with the observed increases in the required dose of levothyroxine.¹¹ Finally, thyroxine absorption, enterohepatic circulation, or other metabolic pathways may be modified in pregnant women, or factors such as redistribution of cardiac output could affect this process. Although these possibilities seem unlikely, especially in early pregnancy, they could be more important during the second half of pregnancy.

Whatever factors are responsible, however, it is clear that the requirement for thyroid hormone increases very early in pregnancy, typically before the first obstetrical visit. There is wide variability regarding the timing of initial and subsequent prenatal visits, and some authorities even advocate fewer such visits.³² If one assumes an initial visit at 10 weeks of gestation (12 weeks after the last menstrual period), 70 percent of our cohort would have been biochemically hypothyroid when first examined. Furthermore, the thyrotropin concentration would have increased in nearly all the women, especially those pregnant by assisted reproductive techniques.

The results of our study suggest that the prevention of hypothyroidism and its possible adverse effects on the fetus and pregnancy in this population requires the combined efforts of primary care physicians, endocrinologists, obstetricians, and the women themselves. On the basis of our observations, we propose a practical solution: women who are currently being treated for hypothyroidism should be given written instructions to increase their current dose of levothyroxine by taking two extra daily doses during each week (i.e., to increase the dose by 29 percent) beginning the week pregnancy is confirmed and to continue doing so until they are able to undergo thyroid-function testing and

obtain appropriate professional guidance. On the basis of our data and those of others, it appears that during pregnancy about 85 percent of women with thyroid dysfunction will require a substantial increase in their usual dose of levothyroxine.¹³ For the 15 percent who do not, a moderate increment would merely suppress endogenous thyroxine production and not lead to thyrotoxicosis. We also suggest that written recommendations be given to all hypothyroid women to request a serum thyrotropin test from health care providers when pregnancy is confirmed. Although this approach may not completely satisfy the increased requirements of athyreotic women, existing data suggest that even partial treatment of gestational hypothyroidism may ameliorate developmental abnormalities.^{4,24}

Thus, levothyroxine requirements increase early during pregnancy in most women with primary hypothyroidism, reaching a plateau after 16 to 20 weeks of gestation at a value about 47 percent higher than the prepregnancy value and persisting throughout pregnancy. Since an increase in the levothyroxine dose was required at a median of eight weeks of gestation and an additional five weeks is required for equilibration of any such change, we suggest that women with hypothyroidism be instructed to increase their usual levothyroxine intake by two additional doses each week immediately on confirmation of pregnancy and to contact their health care provider so that a program of test-guided dose adjustments can be instituted.

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Dr. Larsen reports having served as a consultant for Genzyme and Laboratory Innisba.

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